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ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
07/29/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/836,750	ELIA, JAMES P.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-203,206-236,238-242,244,247,250,251,253,257-263,268-271,280-285 and 288-290.* is/are pending in the application.

4a) Of the above claim(s) *6-203,206-235 and 240-242* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *236,238,239,244,247,250,251,253,257-263,268-271,280-285 and 288-290* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 204, 205, 237, 243, 245, 246, 248, 249, 252, 254-256, 264-267, 272-279, 286, and 287 are canceled. Claims 6-203, 206-235, and 240-242 remain withdrawn from consideration as being directed to a non-elected invention. Claims 236, 238, 239, 244, 247, 250, 251, 253, 257-263, 268-271, 280-285, and 288-290 are under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Rejection of claims 236, 238, 239, 244, 247, 250, 251, 253, 257-263, 268-271, 280-285, and 288-290 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's arguments filed 04/12/2010 have been fully considered but they are not persuasive for the following reasons.

4. Applicant first points out that the previous Office Action did not include an explicit statement of the grounds of rejection, such as in paragraphs 2 and 3, above. The Examiner acknowledges this lapse in formality and apologizes for any confusion it may have caused. It is

noted that the first sentence of the Office Action began with, "In view of the Appeal Brief filed on 06/01/2009…" After the status of the claims was addressed in paragraph 2, paragraph 3 again cited Applicant's Appeal Brief filed 06/01/2009 (first sentence of paragraph 3). Thus, Applicant is correct in concluding that "the Office Action appears to respond to some of the points raised in Applicant's Brief filed on June 1, 2009" (Remarks 04/12/2010, p. 1). Furthermore, "the rejection of record" was cited at the beginning (paragraph 3), not solely at paragraph 68 as Applicant alleges. As of 10/24/2007, the only maintained rejection under consideration has been the rejection of all claims under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

5. Applicant's arguments on pages 4-36 consist of a nearly *verbatim* repetition of the arguments presented on pages 9-46 of the Appeal Brief filed on 06/01/2009, including references to the Office Action mailed on 10/12/2008. The Examiner's responses to Applicant's arguments on pages 4-36 are of record in the previous Office Action mailed 11/18/2009. Therefore, this Office Action will directly address arguments presented on pages 36-65 of Applicant's 04/12/2010 submission.

6. Applicant begins by again taking issue with the treatment of the claims as a group and with regard to their full claimed scope:

> At ¶3 of the Office Action, the PTO confirms its position that all claims must be considered as a group, rather than individually, in the evaluation of enablement. This is patent nonsense. When evaluating enablement, it is incumbent upon the PTO to determine what subject matter each claim recites, i.e., the scope of protection sought for each claim. The scope of dependent claims are properly determined with respect to 35 U.S.C. §112, fourth paragraph. See MPEP Section 2164.08. It is clear that the Examiner's analysis did not treat the subject matter of each claim separately or treat the dependent claims according to statutory mandate.

7. All of the pending claims require administration of a stem cell harvested from bone marrow (e.g. claims 261-263, 268, 269, 288-290), or some factor within the broad genus of growth factors (claims 236,238, 239, 243,244, 247, 250, 251, 253, 257-260, 270,271, 281-285), and growing new cardiac muscle and a new artery. If the narrowest, most specific claims are found to lack enablement, the broader generic recitations must likewise lack enablement. The rejection of record finds that methods comprising these essential and common elements are not enabled by the disclosure, regardless of broad (e.g. "growth factor") or specific (e.g. "living stem cell harvested from bone marrow") limitations. As these essential and common elements are not enabled, it would not be possible for any other limitation to rescue any claim from lack of enablement. Therefore, each claim has been considered, but all claims are rejected on the same grounds.

8. Applicant next argues:

> "At ¶¶ 7-13 of the Office Action, the PTO takes a new position as to the meaning of the claimed term "new artery." Certainly if the present PTO Examiner intended to repeat the prior rejection in total, some mention of this inconsistency should have been mentioned."

9. It is agreed that the paragraphs 7-13 of the previous Office Action presents new arguments based on a reference not previously of record (Buschmann et al., News Physiol Sci. 1999 Jun;14:121-125; hereafter "Buschmann"). It would have been improper to include these new grounds in an Examiner's Answer to Applicant's Appeal Brief. Consequently, prosecution was reopened and a Non-final office action was written. It is not clear why this represents any inconsistency that should require special mentioning. As the previous office action was non-final, Applicant has ample opportunity to respond. In fact, Applicant was notified in the first paragraph that the Office Action would include new grounds of rejection.

10. Paragraphs 7-13 of the previous Office Action included quotations from sections of the specification which address the scope of the term "new artery". Paragraph 12 also discussed the basis whereby Applicant's previous amendment from "forming an artery" to "forming a *new* artery" was taken as distinguishing over the prior art. Paragraph 12 reaches the conclusion that, "Considering all of the evidence, it is reasonable to interpret the claims as encompassing not only extension of new sections of artery from preexisting arteries or arterioles, but also formation of entirely new arterial structures "in the middle of nowhere" so to speak, or *de novo*, in the terminology of the rejection of record."

11. Applicant responds (p.38):

> With such background in mind, the present PTO Examiner now posits a further, different interpretation of a new artery, i.e., that the claims encompass the extension of new sections of artery from preexisting arteries or arterioles and formation of entirely new arterial structures which integrate into an existing artery. Of course, both of the present PTO Examiner's interpretations are disclosed in Applicant's specification and are covered by the claims except those drawn to certain specific artery structures in the newly presented claims.

12. The final phrase, "except those drawn to certain specific artery structures in the newly presented claims" is confusing. Which "newly presented claims" is Applicant referring to? To the Examiner's knowledge, the claims under consideration were last amended on 03/02/2009 and have been the subject of two office actions.

13. Applicant's response characterizes the paragraphs 7-13 as presenting a "different interpretation of a new artery". This might be taken as a criticism, but Applicant ultimately agrees that the Examiner's interpretations are disclosed in the specification and covered by the claims. Thus, although Applicant has expressed mystification as to "why the present PTO Examiner had a need to withdraw the application from appeal and thus compound already developed issues with additional argumentation" (Remarks, page 2), it is evident that in this

instance the protracted process has resulted in a clearer, more accurate understanding of the teachings of the specification and the scope of the claims. The rejection of record finds that, "by teaching that new arteries, or sections of arteries, will grow adjacent to existing arteries and subsequently integrate, the instant specification teaches a novel process that is at odds with the prevailing understanding in the art, as taught in the Buschmann reference. Applicant has now affirmed this interpretation, but argues (Argument p. 39) that "the term "new artery", as described in Applicant's specification, is not limited by its mechanism of formation", and "an inventor is not required to explain the exact theory of the invention". While it is generally true that an inventor is not required to explain the theory of an invention, this does not detract from the finding that, in light of the specification, the **scope** of the term "new artery" includes structures that initially form in the absence of any connection to preexisting arteries. It is maintained that the claims cannot be enabled for the scope of "new artery" defined as in the specification at pages 54, 56, and 62. Further with regard to "theory", in the absence of working examples, the specification necessarily relies on the predictability of the outcomes described in the prophetic teachings. It is maintained that prophetic Examples 18 (p.54), 19 (p.56) and 36 (p. 62) are not credible in the absence of a demonstration that such results did or would occur *in vivo*. This is only one of the reasons why Examples 18, l9, and 36 do not support enablement of the claimed methods. [The fact that these sections of the specification did not suggest that *any* artery formation should be achieved by administration of any kind of cell is an additional point that has been and will be addressed elsewhere].

14. Applicant further attempts to rebut paragraphs 7-13 of the previous Office Action by citing Augustin, *Circulation Research.* 2001;89:645-647. [To aid in discussion, the Examiner is

introducing into the record a fresh copy of this paper. The new copy is more legible than the copy supplied by Applicant, and it retains the page numbers of the original publication.]

Applicant argues:

> In view of the Augustin article, it is clear that all of Applicant's Examples correspond with known medical phenomenon. Hence, the PTO's criticism is flawed.

Applicant's argument appears to be based on "intussusceptive microvascular growth (IMG)" which is discussed in the Augustin article as being a "nonsprouting angiogenesis mechanism". Augustin cites two basic research papers that were published in the same issue of circulation research: Patan *et al., Circ Res.* 2001; 89: 723–731 ("Patan 723") and Patan *et al. Circ Res.* 2001; 89: 732–739 ("Patan 732"). These papers will be entered into the record as they clarify the terminology used by Augustin. The process of IMG is illustrated in Patan 732, Figure 5, which teaches that an elementary loop is formed by lumen evagination around an intervening part of the vessel wall and growth of the loop is achieved by its elongation into the wall of the main vein. This process was suggested for growth of either arteries or veins, but the basic data pertained to veins. It is evident that in both intussusceptive microvascular growth and sprouting angiogenesis the new vessel structure is always connected to, and derived from, an existing vessel; the difference is that in IMG the distal end of the new structure inserts into the existing vessel to form a loop. This process bears no resemblance to the process described in the specification at pages 54, 56, and 62, which respectively teach "a new artery is growing adjacent the patient's original leg artery", "One end of the artery integrates itself in the heart wall to receive blood from the heart. The other end of the artery branches into increasing smaller blood vessels to distribute blood into the heart muscle", and "a new section of artery grows adjacent the original artery. The new section of artery has integrated itself at either end with the original artery".

Regardless of the anatomical locations, these teachings clearly envision new arterial structures which are not initially connected at either end to any preexisting vessel.

15. Further, as noted in the record, Applicant's assertions that post-filing publications of record "confirm Applicant's disclosed and claimed results" cannot be persuasive if "new artery" is defined as in the specification at pages 54, 56, and 62. Although post-filing publications describe methods and results that fall within the scope of the claims under consideration, none of these references support or suggest anything like the formation of a new artery structure which then integrates into an existing artery as taught in the specification. These differences between the prophetic teachings of the specification and subsequent disclosures highlight the speculative nature of the instant specification.

16. Applicant next addresses paragraphs 14-18 of the 11/18/2009 Office Action, which discusses the Strauer reference of record. Beginning in the paragraph bridging pages 40-41, Applicant states:

> Although the PTO continues to rely upon Strauer as evidence of non-enablement, many changes in position regarding why Strauer constitutes evidence that undue amounts experimentation are evident from this record. This lack of a consistent position is exacerbated by constant changes in position by the PTO within this and related applications. Such changes in positions are set forth below. Applicant is uncertain whether or not the present PTO Examiner continues to rely upon such positions. It is especially confusing when contradictory positions are taken in related applications and accordingly, the credibility of the present PTO Examiner is diminished.

17. The Office Action mailed on 09/22/2006 included the following on page 9:

> 1) In the instant case, the quantity of experimentation required would be very large. Applicant's attention is directed to pp. 1916 to 1918 of Strauer (of record, 2002, Circulation 106:1913-1918), who review the crucial questions that had to be addressed while designing and realizing their trial of administering stem cells to human patients to repair damaged heart tissue. These included decisions regarding what cell population to use, what delivery method to use, and when cells should be transplanted. As can be seen from pp. 1916-1918, these were not simple or routine matters and involved great quantities of experimentation. In fact, one can see that the determinations of these details

involved the act of invention.
2) The specification provides no guidance along the lines of the details worked out by Strauer.

18. In view of the above, it is difficult to understand why Applicant would say "In the Office Action, the PTO now apparently takes the position that the mere designing of the Strauer trial regarding cell population, administration technique, and transplantation timing somehow constitutes evidence of undue experimentation" (Argument p.41) as if this position were something new or contradictory to the record. These same grounds with respect to the Strauer references have been maintained throughout all prosecution for the past 4 years. Additional references have been cited to elaborate upon and further support the arguments and to rebut Applicant's arguments.

19. Applicant argues (p.40):

> "...the present PTO Examiner appears to mischaracterize Strauer as "...a published report of the results a human clinical trial .... " While there is no information in the Strauer publication to support such characterization, it is not credible to imagine or assert that clinical trial reports would not include all data generated during the test procedures. If Strauer constitutes evidence of undue amounts of experimentation, such evidence would be reported. Thus the Examiner's reliance upon Strauer in this regard amounts to rank speculation and puffery. It is beyond the pale to assert that results have been deliberately withheld based solely on the present PTO Examiner's assertion. What is glaringly absent in this record is the present PTO Examiner's answer to Applicant's challenge to provide a Declaration attesting to the fact that he was a party to or was personally aware of such practices in the medical field."

20. The charge of mischaracterizing Strauer is also alluded to on page 59 of Applicant's arguments. This is puzzling because Applicant has previously stated, "A careful reading of Strauer reveals that work performed during a Phase I trial was used as a basis for the article." (Appeal Brief filed 06/13/2005, page 40). Strauer clearly reports the results of a trial to test the feasibility of cell treatments in humans.

21. Applicant's reference to an assertion that "results have been deliberately withheld" stems from a mischaracterization of one aspect of the rejection of record which finds that that "In peer-reviewed journal articles, failed experiments are generally not reported, and thus when the

successful regimen is disclosed, it cannot be concluded that no experimentation was done" (Examiners Answer 01/24/2008, p.20). [Note that this speaks to the original proposition that Strauer represents evidence of experimentation]. In response to Applicant's objection to this, the office action mailed on 10/02/2008 (paragraph 15) included documented evidence, including a peer-reviewed study and a Web-based forum associated with the highly respected journal, *Nature*, to show that there are many good reasons to believe that relying solely on the printed words in a publication would lead to an underestimation of the amount of work that was actually done. There has been no assertion of deliberate withholding of results as Applicant insinuates. The 11/18/2009 Office Action (paragraph 18) expressly pointed out that the documented evidence supports the original finding without reliance on any official notice or personal experience on the part of the Examiner. Therefore "Applicant's challenge to provide a Declaration attesting to the fact that he was a party to or was personally aware of such practices in the medical field" is an irrelevant attempt to divert the focus of discussion away from the merits of the case. Furthermore, it was conceded that this issue would naturally be more significant in basic science and preclinical research than in a report such as Strauer et al. 2002, which is based on a human trial. Applicant's response seems not to have noticed this concession in partial agreement with Applicant's prior arguments with respect to Strauer *per se*.

22. It cannot be disputed, however, that published scientific papers represent actual experimentation and that when work based on actual experimentation is reported in a scientific journal, not every detail from the laboratory notebook makes it into the final draft. This remains important in considering whether Strauer constitutes *evidence of* extensive experimentation. Applicant has previously argued that "it is clear from Strauer 2002 that, at the pages referred to

by the Examiner [pages 1916-1917], Strauer 2002 appears to have relied upon the prior work of others, including the selection of cell population, rather than upon experimentation" (Reply Brief filed 03/18/2008, Applicant page 15. Emphasis added here). Applicant now argues that "If Strauer constitutes evidence of undue amounts of experimentation, such evidence would be reported." Paragraphs 15-17 of the 11/18/2009 Office Action made the point that Strauer et al. explicitly disclosed their reliance upon the prior work of others. Prior work was considered in the selection of cell population and determining the timing of cell administration. (Of course, the experimentation relied upon was "prior" to the Strauer study, but "post-filing" relative to the instant application). Contrary to Applicant's repeated assertion (Argument, p. 41), paragraphs 14-18 of the 11/18/2009 Office Action did point to a specific teaching in support of the proposition the Strauer considered determination a cell population to be critical—see the quote from Strauer, p.1916 in paragraph 15, which explicitly lists "What cell population should we deliver?" as the first of 3 crucial questions to consider. Note also that this same teaching was cited in the Office Action mailed on 09/22/2006, quoted above. Strauer similarly identified "When should the cells be transplanted?" as a critical question. Applicant's arguments on pages 41 to the top of page 44, and in the paragraph bridging pages 47-48, rely on the untenable position that the basic and preclinical studies cited by Strauer do not represent experimentation. It does not matter whether Strauer et al. performed the preclinical experimentation or the work was done by others. What matters is that the successful method relied upon prior experimentation, and it could not be carried out on the basis of the mere suggestion that "a patient's own cells" may be used to form an artery, among other possible outcomes (Specification, pages 47-48). Likewise, it does not matter whether Strauer ultimately found that

"there is no requirement for using a specific subset of bone marrow stem cells" or that a broad range of timing of cell administration after damage to the heart is permissible (Argument, p. 43). These conclusions were reached only in view of Strauer's results and the work of others cited by Strauer, and they were not predicted by the assertion that "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques" can be genetically engineered to form entire organs such as a tooth, kidney, or eye, depending on the genes used (Specification, Examples 11-17).

23. Applicant next addresses paragraphs 19-28 of the 11/18/2009 Office Action. Applicant first mischaracterizes the office action in order to allege inconsistency:

> "…the PTO continues to contend that Applicant does not disclose that stem cells are useful in the practice of the claimed invention. However, in ¶53 of the Office Action, the present PTO Examiner curiously admits that "Therefore, the most Applicant can say about the instant disclosure is that, by circuitous logic not explicitly presented in the disclosure, one of skill in the art might surmise that a method to use autologous stem cells to grow an artery was suggested.""

24. A more accurate summary of paragraphs 19-28 would acknowledge the following:

> "Even if interpreted in Applicant's most favored light, the most precise description of the cells to be administered in the instantly claimed methods is "bone marrow stem cells". **The instant specification refers to bone marrow only in the sentence, "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques"**, which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10). Thus, the specification suggests that three sources of stem cells are equivalent to one another for purposes of the disclosed methods (¶20).
>
> "In total, the teaching of the specification does not give the skilled artisan clear instructions for what to do" (¶24).
>
> "It is evident from Stauer and Kornowski that the critical cell in the preparations they administered may not be any previously characterized stem cell; it may not even be a *stem cell* at all but rather some other previously uncharacterized growth factor secreting cell" (¶26).

25. None of this is inconsistent with the quote from paragraph 53, nor can it be logically interpreted as contending that Applicant does not suggest the use of stem cells for a various

purposes. Among the principal findings of paragraphs 19-27 are: (1) as noted, the teaching of the specification does not give the skilled artisan clear instructions for what to do (paragraph 24) and (2) there is no basis in fact for any arguments or assertions that the instant specification distinguishes over prior art, or that post-filing art confirms the instant teachings, on the basis of an alleged novel recognition that unfractionated bone marrow mononuclear cells can be used to grow an artery (paragraph 25).

26. Applicant responds with quotes that are attributed to "The Third Supplemental Declaration of Dr. Andrew E. Lorincz and the Fourth Supplemental Declaration of Dr. Richard Heuser, at paragraphs 4, 5, and 7" (p. 44-45). However, the paragraphs provided in Applicant's argument do not correspond to the Declarations that were submitted on 04/12/2010. The presented paragraphs appear to be identical to Declarations that have been addressed in the record. As noted in paragraph 63 of the 11/18/2009 Office Action, the Declarants of record have been willing to say: "The disclosures referenced in above Paragraph ... of the specification *relate to* using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery" (emphasis added)." That is, the Declarants managed to piece the general idea of the instant claims together. According to the Declarations, this general conclusion was based upon reading juxtaposed excerpts of the specification (not the complete specification) together with claims reciting administration of stem cells to grow an artery, which were not original to the application as filed. A disclosure that makes it possible to piece the claimed generic concept together is not the same as an enabling disclosure. It is easy to predict that if one injects cells into a body, *something* will grow therefrom; it might even be an artery—even tumors have arteries.

27. Applicant next argues that "The PTO erroneously considered that the specification did not disclose the concept of using unfractionated bone marrow mononuclear cells to grow an artery" this time correctly citing Paragraph 8 in the Fourth Supplemental Declaration of Dr. Heuser and the Third Supplemental Declaration of Dr. Lorincz. These Declarations were signed by the respective Declarants on 01/17/2010 and 02/02/2010, first submitted on 04/12/2010, and they have not been previously considered. As the Declarations relate to the subject at hand, their consideration is included within the context of the present rejection, as follows.

28. The Declarations Dr. Heuser and Dr. Lorincz under 37 CFR 1.132, filed 04/12/2010, are insufficient to overcome the rejection of claims 236, 238, 239, 244, 247, 250, 251, 253, 257-263, 268-271, 280-285, and 288-290 based upon failing to comply with the enablement requirement under 35 U.S.C. 112, first paragraph, as set forth in the last Office action for the following reasons:

29. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, 1) the nature of the fact sought to be established, 2) the strength of any opposing evidence, 3) the interest of the expert in the outcome of the case, and 4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

30. There is no evidence that the experts have an interest in the outcome of the case.

31. The nature of the fact to be established is concerned with one aspect of the rejection of record in which it is found that the specification does not provide adequate guidance with regard to the choice of cells to be administered in the claimed methods. Paragraphs 7 and 8 of the Declaration are specifically directed to the scope of the expression "stem cells harvested from bone marrow" as it would be understood by a person of skill in the art at the time the instant application was filed in 1998.

32. The Declarants in paragraph 7 express an understanding "that it was commonly known at the time of the Elia invention, April 21, 1998, that bone marrow comprise stem cells that are pluripotent in that they are capable of forming multiple tissue types." This is not disputed. The Declarants stress in paragraph 7 that it is not possible to cause artery formation by implanting only CD34+ endothelial progenitor cells into a human patient because CD34+ endothelial progenitor cells are unipotent and do not differentiate into smooth muscle cells. In paragraph 8, the Declarants express an "understanding that as of circa the date of the Elia invention those skilled in the medical arts did not limit the scope of the term bone marrow stem cells to a subset of mononuclear cells composed of CD34+ endothelial progenitor cells." This understanding is not disputed. The record in this case does not include any suggestion or allegation that the term "bone marrow stem cells" should refer only to a subset of mononuclear cells composed of CD34+ *endothelial* progenitor cells.

33. In paragraph 8, the Declarants express an understanding that "the language "stem cells harvested from bone marrow" as defined in the written disclosures above-mentioned patent applications and claims to encompass the entire population of bone marrow mononuclear cells and cellular components, including a range of cytokines, in contrast with any fractionated population of such cells." Declarants further express the *opinion* "that one skilled in the medical arts reading the application at

the time of filing, April 21, 1998, would have understood that the language was intended to describe a composition comprised of the entire population of bone marrow cellular components. To conclude otherwise, specifically in the absence of explicit direction to conduct a fractionation of cells, would require such a skilled person to ignore the decades of use of such language in the medical arts, particularly in regard to the practice of treating patients with bone marrow transplants".

34. Opposing evidence has been discussed on the record. It has been acknowledged that the instant specification does not teach that there is anything critical about how to prepare bone marrow stem cells (paragraph 25 of the 11/18/2009 Office Action). The issue is what effect this absence of explicit direction would have on the guidance perceived by one of skill in the art reading the specification. A point made it the rejection of record, but not addressed by the Declarants, is that the manner in which bone marrow stem cells are discussed in the specification logically teaches away from any suggestion to use unfractionated bone marrow. It is again emphasized that **the instant specification refers to bone marrow only in the sentence, "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques"**, which appears three times (page 40, lines 27-28; page 41, lines 23-24; page 42, lines 9-10). Thus, the specification suggests that three sources of stem cells are equivalent to one another for purposes of the disclosed methods. It was still unclear long after the instant specification was filed whether circulating blood contains any mesenchymal stem cells or other marrow-derived cells with broad potential (Roufosse *et al*., Int J Biochem Cell Biol. 2004 Apr;36(4):585-597 of record; see especially section 3, pp. 588-591, Table 2, and section 6, p. 394). Therefore, by listing "stem cells harvested from the blood of the patient" as an equally usable alternative of "stem cells harvested from the bone marrow", the specification teaches away from the suggestion that the bone marrow cells necessarily include mesenchymal stem

cells. The instant specification does not mention mesenchymal stem cells, even once. Trigg (Pediatric Transplantation, 2002 Dec;6(6):465-474) submitted by Applicant with the Appeal Brief filed 06/13/2005, teaches that 30 years of experience with transplantation had shown that "stem cells collected from peripheral blood were somewhat different from those collected from the marrow space" (p.470, left column). If the specification teaches that "stem cells harvested from the blood of the patient" are equivalent to "stem cells harvested from the bone marrow" for purposes of the claimed methods, and it is known in the art that stem cells in blood are different from stem cells in the marrow, and that blood does not comprise the complete set of pluripotent cells found in marrow, it is illogical to conclude that the *specification intends* "stem cells harvested from the bone marrow" to mean the "entire population of bone marrow mononuclear cells and cellular components, including a range of cytokines".

35. The possibility should be considered that in casual conversation, or in situations where precision is not needed, persons of skill in the art may refer to a "stem cell transplant" when the actual procedure under discussion employed unfractionated bone marrow or the entire mononuclear fraction. Conversely, one might say "bone marrow transplant" when the patient received only mononuclear cells or selected stem cells. This would account for the Declarants' stated conclusion despite the logical inconsistency described above. In this view, it is plausible that Applicant had unfractionated bone marrow in mind when writing "stem cells harvested from the bone marrow". Other than the instant specification, no examples of such imprecise language have been made of record, however. The evidence of record does include, however, examples which show that when details matter, it is common practice to use a generic term such as "bone marrow" or "bone marrow cells" when little or no fractionation is done, and to use the term

"stem cells" when referring to the actual stem cell population. For example, when Janssen *et al.*, (Journal of Hematotherapy, 1:349-359 (1992)) describe use of an apparatus for processing of bone marrow stem cells, the definitive demonstration that "stem cells" were obtained was by identification of CD34+ cells or by colony forming assays; prior to that the cells were simply referred to as fractions obtained in a step of isolation (mononuclear, Ficoll gradient, buffy coat, etc., see Figures 10 and 11 and Table 1). The claims of the Kornowski '832 patent of record recite administration of *bone marrow aspirate* to induce collateral blood vessel formation in the heart (see claim 1). Similarly, Strauer (2002, of record) acknowledges that bone marrow contains stem cells, but uses the generic term "bone marrow cells" to describe the population of bone marrow mononuclear cells used for transplantation (see Abstract and text on page 1913). Applicant has repeatedly asserted that the instant specification teaches administration of the same cell population used in the Kornowski patent and the Strauer publication. Similarly, Applicant has asserted that the Dohmann reference of record discloses the process, materials, and results which correspond to the claimed invention. Dohmann administered "autologous bone marrow mononuclear cells" (see title). It is clear that Kornowski, Strauer, and Dohmann were precise in their descriptions and they did not use a term that denotes a subpopulation of cells (stem cells) when they were trying to communicate that little or no fractionation was performed.

36. Finally, there is a question of the presence or absence of factual support for the expert's opinion. Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). All of the arguments, evidence, and references cited above were available to the Declarants prior to the dates the Declarations

were signed. The Declarants did not specifically address any of the arguments, evidence, and references of record, nor did they offer any factual evidence to support their expressed opinions. Even if published examples which conform to the Declarants' opinions, *i.e.* wherein the expression "stem cells harvested from the bone marrow" means "entire population of bone marrow mononuclear cells and cellular components, including a range of cytokines", were to be found, this would not negate the point made in the rejection. The evidence of record establishes that at least some persons of skill in the art carefully distinguish "stem cells" from "the entire population of bone marrow cellular components" when they aim to provide information that would enable others to reproduce their results. Therefore, in the absence of further explanation or a working example, the expression "stem cells harvested from the bone marrow" does not clearly guide the skilled artisan to the choice of either unfractionated marrow or the mononuclear fraction. Thus, the declarations have been fully considered and the rejection is properly maintained based on consideration of the preponderance of the totality of the evidence.

37. In the paragraph bridging pages 46-47, Applicant asserts that the "PTO also erroneously relies upon Ziegelhoeffer as evidence that stem cells do not differentiate into arteries as disclosed and claimed by Applicant and concludes that even though Dohmann and Strauer teach artery growth it was not via differentiation." Paragraph 28 of the 11/18/2009 Office Action cited Ziegelhoeffer to argue that the prediction that ""if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (specification p.48, lines 13-15) has been shown not to be true when the source of stem cells is a mixed population of bone marrow cells and the organ under consideration is a new

artery." Applicant disparages the Ziegelhoeffer reference because it relied upon an animal model. It is evident that the editors of "Circulation Research, Journal of the American Heart Association" deemed the Ziegelhoeffer study sufficiently relevant to human conditions to be worthy of publication. Applicant further points out that "Strauer 2005 teaches that differentiation may be one of four identified mechanisms via which bone-marrow stem cells express their regenerative potential for the treatment of infarctions in human patients." This is followed by a quote from Dr. O'Neill attesting to our ignorance of the basic science with regard to the cascade of processes that actually allow a new cell to come in and regenerate. All of this attests to the unpredictability of biological processes, which is particularly important in determining enablement under 35 USC 112(1). In contrast to Dr. O'Neill's humble expression, Applicant had argued repeatedly, and with *certainty*, that stem cells are able to promote tissue growth or formation of an artery through "differentiation and morphogenesis". Applicant's present argument may be convincing to the point that direct differentiation has not been *disproved* when the source of stem cells is a mixed population of *human* bone marrow cells and the organ under consideration is a new artery in a *human*. However, in view of the uncertainty and lack of knowledge in the field, Applicant's repeated reliance on "differentiation and morphogenesis", supported by a single sentence in the specification, p.48, lines 13-15, does not make for a convincing argument that post-filing disclosures confirm the teachings of the specification.

38. It is noted that Applicant's arguments from the middle of p.45 to p.47 are repeated *verbatim,* except for the O'Neill quote, on p. 50 to the top of page 52. The paragraph in the

middle of page 47 is essentially repeated in the paragraph bridging pages 51-52 and again in the paragraph bridging pages 52-53.

39. On page 48, Applicant addresses the two Journal of Invasive Cardiology online articles that had been discussed at paragraphs 30-32 of the Office Action. Applicant asserts:

> It is noted that the present PTO Examiner has not yet provided an explanation as to why only abridged versions of the two articles were furnished, especially in view of the high degree of relevance to the issue of enablement of the missing portions.

40. This is not an accurate description of the record. In paragraph 30, the Examiner explicitly acknowledged having failed to recognize an error in converting the web pages to pdf format, which resulted in the being documents incomplete. The accidental nature of this omission was attested by the fact that the text of the rejection included a quote that was not reproduced on the copies provided. Applicant clarified the record by supplying complete copies as exhibits A and B with the Appeal Brief Filed 06/01/2009.

41. Most of Applicant's further present comments regarding these publications are the same as those addressed at paragraphs 30-32 of the previous Office Action. A new question is raised on page 49, where Applicant asks, "What is the point of such second guessing?" referring to the prior speculation as to what Dr. Heuser, a Declarant of record in the present case, said and did not say in the published discussion. The point is that the gist of Applicant's argumentation with respect to the rejection of record, especially including argumentation based on the Heuser declarations, is that the controversies under discussion have been solved or rendered trivial by Applicant's disclosure. The rejection posits that *if Applicant's arguments are to be accepted*, then Dr. Heuser, having "read and understood" the instant specification, was in possession of information significant to the controversies under discussion. *If so*, Dr. Heuser could have

clarified matters without divulging any confidential information by directing his colleague's attention to published disclosures. According to Applicant's arguments, Dr. Heuser could have explained that all one needs to know about how to grow cardiac muscle and new arteries is that "a patient's own cells" may be used to form an artery, among other possible outcomes (Specification, pages 47-48) and that "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques" can be genetically engineered to form entire organs such as a tooth, kidney, or eye, depending on the genes used (Specification, Examples 11-17). There may be any number of reasons why Dr. Heuser chose not to bring the instant specification into the discussion. A further purpose of the statement "One wonders why Dr. Heuser did not speak up and enlighten his colleagues" (Office action 10/02/2008, paragraph 48) was rhetorical, aimed at encouraging all readers of this record to contemplate what would have happened had Dr. Heuser chosen to provide his colleagues with *verbatim* quotes from the instant specification.

42. Applicant next argues (p.48):

> At ¶29 of the Office Action, the PTO laboriously considered whether or not Applicant was the first to disclose and claim a method for human heart repair by implanting cells, such as stem cells, and growing a new artery. Of course, such issue has no bearing upon the instant enablement rejection. The present PTO Examiner has insisted that such first to disclose and claim was in the post-filing Kornowski application WO/2000/057922. The simple answer to this non-relevant issue is that, being that Dr. Elia was the first to disclose the claimed invention, it follows that Dr. Kornowski could not have been the first to disclose and claim such invention.

43. Applicant is quite correct that a question of priority of disclosure should not have a bearing on an enablement rejection. Nevertheless, the record shows that Applicant had included an assertion of being "the first to disclose and claim a method for human heart repair by implanting cells, such as stem cells, and growing a new artery" in arguing the question of enablement (Brief filed 06/01/2009, p.36). Paragraph 29 was included in the previous office

action for the expressed purpose of clarifying the record. Paragraph 29 **did not** say that WO/2000/057922 was the first to disclose and claim a method for human heart repair by implanting cells. The point is that the first *claims* to a method for human heart repair by implanting cells were asserted in WO/2000/057922. It follows that Applicant could not have been the first to disclose *and claim* such invention. Paragraph 29 did not dispute that Applicant's filing date precedes that of WO/2000/057922. Paragraph 29 did not directly address the question of whether Applicant's earlier filed specification constitutes disclosure of "a method for human heart repair by implanting cells, such as stem cells, and growing a new artery" in full compliance with the requirements of 35 USC 112(1).

44. Further on page 49, Applicant argues:

> At ¶¶33-41 of the Office Action, the PTO took issue with whether the post-filing publications and patents "confirm" the teachings of the instant specification. In the argumentation of this erroneous conclusion, the PTO, at page 23 of the Office Action, seems to believe that "...the very concept of the claimed methods relies on selection of seemingly unrelated portions of the specification and putting them together without specific prompting to do so." The fact that Drs. Heuser and Lorincz had no difficulty in reading these portions and concluding that the specification was adequate to teach one skilled in the art to make and use the invention should dispose of this issue. The present PTO Examiner, however, apparently does not possess the comparable skill and thus should accept the evidence proffered by those skilled the art, such as the Declarants

45. Of the paragraphs cited by Applicant, paragraph 33 first summarized the preceding paragraphs dealing with the issue of whether post-filing references confirm the teachings of the instant specification. Paragraphs 33-41 then dealt with the direction provided by the instant specification and included reproductions of the sections of the specification relied upon by Applicant. These paragraphs find that the very concept of the claimed methods relies on selection of seemingly unrelated portions of the specification and putting them together, without specific prompting to do so. Applicant response with respect to Drs. Heuser and Lorincz has been addressed in the record, at least at paragraphs 53 and 64 of the previous office action. The

Declarants of record have been willing to say: "The disclosures referenced in above Paragraph ... of the specification *relate to* using a growth factor for promoting the growth of soft tissue, and more specifically, to a method of using a cell, *such as* a stem cell, to grow soft tissue, *such as* an artery" (emphasis added)." According to the Declarations, this general conclusion was based upon reading juxtaposed excerpts of the specification (not the complete specification) together with claims reciting administration of stem cells, which were not original to the application as filed. It is a separate question whether the specification *as filed* supports the claimed concept and it is yet another whether question as to what extent the said concept, if present in the specification, enables one of skill in the art to make and use the claimed invention.

46. Paragraphs 33-41 of the previous office action pointed out that pages 40-42 of the specification comprise the only references to bone marrow in the entire specification. These Examples assert that whole organs can be grown from "Living stem cells are harvested from the bone marrow, the blood of the patient, or from cell culture techniques", if said cells are contacted with certain genes. These examples do not set forth credible procedures to produce the results asserted within the examples, and they do not even mention growth of an artery or repair of a heart as recited in the instant claims. Nevertheless, Applicant expects the skilled artisan to take the mention of bone marrow in the context of Examples 11-17 and combine it with the mention of "growth of an artery" (among other possible outcomes) on page 48 to arrive at enabling support for the instant claims. Referring to Applicant's choice of pages 47-48, it was pointed out that this section begins with a general statement that organs and/or tissues can be formed utilizing the patient's own cells. It was further pointed out that the disclosed example of a "patient's own cells" is not "stem cells harvested from bone marrow", but instead is a skin cell(s) is removed

from the intraoral lining of a cheek. It is this skin cell that is the subject through all the description leading up to the mention of artery formation. "Germinal cells" are suggested as an alternative to the dedifferentiated skin cells but since "germinal cells" are defined only by function, the specification does not guide the artisan as to where or how to obtain the cells that can be used to grow an artery or any other organ. In order to arrive at the claimed methods, one first has to select "growth of an artery" from among the several possible outcomes suggested, select "new portion of a pre-existing heart", and then guess that the "some cases" where stem cells are utilized (p.48, line 13) refers to instances where one wishes to grow an artery in a dead or damaged heart. Even if that guess is made, no particular reason is given why the stem cell should be harvested from bone marrow—bone marrow is not mentioned in the context of artery formation or heart repair. Since the artisan is required to look elsewhere in the specification for guidance as to which cell to use, one finds on page 37, lines, 19-23 teaching that would have the skilled artisan believe that any cell can be made to form any tissue, which teaches away from any suggestion to specifically use stem cells to form an artery. Applicant's only additional response is to assert that these facts and arguments in nine paragraphs from the previous office action should be ignored because the Examiner is not qualified to disagree with the Declarants. It is evident, however, that the sweeping generalizations in the specification could be interpreted as teaching almost anything. The Declarants could just as easily have opined that "the disclosures referenced in above Paragraph" of the specification *relate to* using a stem cell from the blood to grow a kidney, to using a dedifferentiated skin cell to grow pancreatic islets, or to using any sticky cell to grow an entire new heart.

47. This directly relates to Applicant's next argument on page 53:

> At ¶¶43-44 of the Office Action, the PTO continues to maintain that it is not clear "how to use stem cells" in the claimed invention. The simple answer is to place such cells in the body of a human patient and then achieve the claimed result thereby. Does the present PTO Examiner actually not understand that a simple injection of stem cells harvested from bone marrow into or adjacent a human heart will result in the growth of arteries and cardiac muscle?

48. In view of the paragraphs 34-43 of the previous office action, and the preceding paragraphs herein, it is legitimate to ask, "Where does the specification say that one of skill in the art should inject stem cells harvested from bone marrow into or adjacent a human heart in order to grow arteries or cardiac muscle?" Furthermore, since the specification teaches that stem cells may produce any desired tissue, how does one how does one specifically grow arteries or cardiac muscle? Applicant cannot say that the specification teaches that pluripotent cells will respond to local cues to yield the desired tissue: According to Applicant's interpretation, the specification at p.37, lines, 19-23, teaches that it is the *stem cells* that provide required signals. Paragraphs 43-44 the previous office action further emphasized that the prediction that "if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (p.48, lines 13-15) has been shown not to be true, or at least in doubt, when the source of stem cells is a mixed population of bone marrow cells and the organ under consideration is a new artery (see Ziegelhoeffer et al., (*Circulation Research* 2004;94:230-238).

49. On page 52, Applicant takes issue with the way certain teachings of the specification have been treated in the record:

> At ¶42 of the Office Action, the PTO continues to disparage the use of and misapprehend the meaning of "cascade of genetic material." The present PTO Examiner has taken many inconsistent and contrary positions in the prosecution of Applicant's applications regarding the meaning of the term "cascade of genetic material." Initially the term was disdainfully deemed as "nonsense," and when Applicant presented evidence of the use of essentially similar terms in the art (such as in the portion of the O'Neil publication omitted by the present PTO Examiner and called to attention by Applicant), the present PTO Examiner then conveniently switched his position to deem Applicant's verbiage as a malapropism. Should further education be warranted,

> Applicant hereby again refers the present PTO Examiner to Augustin. Dr. Augustin utilized the term "angiogenic cascade" in connection with the formation of new vasculature. Applicant points out that Dr. Elia and the other above-cited publications do not use the exact wording, but the same meaning and communication is evident. If Applicant's wording is a malapropism, which of the other wordings is correct and which are also malapropisms? This situation is illustrative of the PTO's record of shifting positions and pursuing non-relevant issues.
> The PTO, in an uncharacteristic attack on procedural due process normally accorded applicants, asserts that the instant specification provides "nonsensical" direction to one skilled in the art.

50. First, it must be emphasized that these issues are relevant to the statutory requirement that the specification should set forth a description of the manner and process of making and using the invention, "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same". The record shows that the characterization of "cascade of genetic material" has been refined from "makes no sense" to "malapropism' in response to Applicant's continued refusal to understand the difference between "material" and "processes". For further explanation, Applicant is referred to the office action mailed 07/24/2007 in parent application 09064000, incorporated by reference in its entirety, at paragraphs 19-22.

51. Applicant's second issue on page 52 apparently refers to the finding that "In Examples 11-17 the artisan is instructed to remove genes from skin tissue of a patient and then the artisan is given the nonsensical instruction to store the genes in nutrient culture medium" (Office Action mailed 11/18/2009, paragraph 35). Other than to complain of an alleged "attack on procedural due process" Applicant does not provide any argument or evidence that an instruction to store a nucleic acid in nutrient culture medium would make any sense to a person of skill in the art. Applicant's specification speaks for itself in this matter. This failure to accurately render the simple technical procedure of storing DNA undermines the credibility of Examples 11-17, which

in any case are incredible for predicting that whole organs will grow from cells that have been placed in culture medium together with the stored genes.

52. On pages 53-56 Applicant continues with the argument:

> At ¶¶45-53 of the Office Action, the …present PTO Examiner continues to erroneously consider that cells and genes are not defined by the instant specification as species within the genus "growth factors… Such erroneous position is at odds with the prior statements of Examiner Kemmerer in the prosecution of this and other related applications of Applicant. Such gross inconsistency in this and other issues obviously renders it difficult for Applicant to understand and respond to the instant Office Action.

53. Applicant's present arguments are not new and they have been already addressed in the previous office action. Applicant's difficulty appears partly due to Applicant's conflating the concepts of restriction/election with the enablement issue at hand. If an examiner is presented with claims reciting cells to be a species of growth factor, the examiner would expect to be able to take the claims at face value and restrict the claims accordingly. It is a separate question whether the specification as filed supports the claimed concept and it is yet another whether question as to what extent the said concept, if present in the specification, enables one of skill in the art to make and use the claimed invention. Even if it is conceded that in the lexicon of this specification, 'cells' may be a subgenus of 'growth factor', this would not provide any justification for asserting that any time any growth factor is mentioned, the skilled artisan is prompted to apply the teaching to cells in general, or specifically to stem cells. As stated in Paragraph 49 of the previous office action, the "restriction requirement indicates that cell therapy and gene therapy are not obvious variants of one another, as indicated, for example, by their separate classifications. It follows that an example directed to gene therapy would not make obvious, or implicitly suggest a method of cell therapy. Any such suggestion would need to be explicitly made." This would be true even if only the genus of well known polypeptide growth factors is

considered. The term "growth factor" comprises polypeptides with diverse and non-overlapping activities. Upon learning that a particular previously known growth factor can produce any particular effect, one of skill in the art would not assume or predict that any other growth factor should have the same effect. For example, a demonstration that VEGF stimulates angiogenesis would not, by itself, cause a person of skill in the art expect that EGF, NGF, or HGF would also cause angiogenesis. Even if the VEGF results were accompanied by an *assertion* that EGF, NGF, or HGF should behave like VEGF, this would not be accepted without a demonstration or a strong argument based on previously known effects. The present specification compounds the complexity by expanding genus of "growth factors" to include, apparently, all of the molecules that are generally recognized as growth factors, plus all of the genes encoding such molecules (although genes are not mentioned in the definition on pages 20-21 of the specification), plus all living organisms, and unspecified organic and inorganic matter. The specification further teaches that administration of VEGF cDNA should have arteriogenic activity beyond that which was previously ascribed to it (see paragraphs 28, 43, and 50 of the previous office action).

54. The rejection of record finds that the specification should provide a clear path that leads from one species to the other, if that indeed was Applicant's original intent. (The original intent is not clear: Applicant is referred to the office action mailed 01/14/2010 in parent application 09064000, incorporated by reference in its entirety, at paragraphs 12-15. The earliest claim reciting administering cells to repair a heart in any continuing, divisional, or continuation-in-part of Application No. 09064000 was entered in the present application on 04/17/2001 (claims 36, 39, and 40). The first claims reciting "living stem cells harvested from bone marrow" were introduced in the present case on 11/21/2005.) Instead, the line of reasoning leading from

"VEGF cDNA" (in examples 18, 19, and 36) to "growth factor" to "stem cell" requires the skilled artisan to perceive that the specification intends the broadest definition "growth factor", which includes "living organism", and then select the subgenus "cells" from the genus of "living organisms", and then to further select subgenus "stem cells". The requirement for this indirect line is important to description of the manner and process of making and using the invention, "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same" as required by statute, independently of any requirement for restriction or election of species. This finding does not violate or contradict any past or present restriction requirement in this application or any related application. To elaborate upon (not "contradict") the quotation from Examiner Kemmerer's February 22, 2006 Office Action, Applicant's definition of "growth factor" is "not relevant" because it is not effective to guide the skilled artisan in performing the claimed methods involving administration of the elected species of cells.

55. Applicant asserts, beginning on page 56:

> "At ¶¶ 54-59 of the Office Action, the PTO continues to misunderstand the use of the well established, art recognized conversion technique utilized by Applicant and recognized by Drs. Heuser and Lorincz. The PTO's *ad hominem* criticism of Applicant's conversion set forth at fails to adequately give weight to its evidentiary value."

56. This is not persuasive, first, because the evidentiary value of Applicant's conversion has been thoroughly considered on the record. See for example the previous office action at paragraphs 55-59 and the office action mailed 10/02/2008 at paragraphs 24-33. Applicant had previously made the assertion that the specification describes new artery growth and heart repair by direct injection of growth factor cells in dosage ranging from approximately 6.25×10^6 (Example 18 & 36) to approximately 12.5×10^6 (Example 19). When confronted with the fact

that no such teaching can be found in the specification (the cited examples do not mention cells at all), Applicant instead asserted that these cell number values are readily obtained because one of skill would extrapolate an appropriate cell number from the quantities of plasmid DNA taught in the Examples (Brief filed 06/01/2009, p.31). Applicant's present arguments are duplicative of arguments that have been addressed thoroughly in the record. It is clear from the facts presented in the record that the method under discussion, which purports to extrapolate an appropriate cell number for administration from the disclosed quantities of plasmid DNA, is Applicant's *post hoc* derivation. It is not present in the application as filed. It is not implicit in the teachings of the specification. It is not substantially analogous to well known methods of converting DNA amounts to cell numbers within a species cited by the Declarants. It is not information that is already known by those skilled in the medical arts. It is not based on sound reasoning based on the information of record. There is no example of it in the prior art or post-filing art. There is no rational basis for proposing that a person of skill in the art at the time the instant application was filed would even think of doing it without being specifically prompted to do so. The instant specification does not provide that prompting. Each of these findings is supported by facts and references. Therefore, Applicant's present assertions regarding "lack of any evidence" and "unsupported opinion" (Arguments, p. 58) are not supported by the record.

57. Likewise, Applicant's assertion that "Applicant has already provided two instances of the conversion in regard to Strauer and Isner" (p.58) is not supported by the record. As pointed out in paragraph 56 of the previous office action, there is no evidence that Isner saw any significant relationship between the disclosed amounts of plasmid DNA and numbers of cells. Furthermore, close inspection of the numbers disclosed in Isner shows that even if using the amount of

plasmid DNA to calculate a number of eukaryotic cells were a legitimate procedure, the formula for doing so could not be the simple ratio Applicant has presented if the formula is based on Isner's numbers. The record also shows that Strauer did not recognize or perform any conversion related to that asserted by Applicant. Furthermore, the record finds that any relationship between the results of Applicant's formula and any cell number taught in Isner '887 or in Strauer, or any post-filing art is coincidental. It is neither surprising nor convincing that a formula could derive a value with the trillion-fold ranges of cells taught in Isner or Strauer.

58. Secondly, Applicant's argument is not persuasive because the criticism of record of Applicant's conversion is not *ad hominem*.

> Ad hominem 1.(*logical fallacy*) A fallacious objection to an argument or factual claim by appealing to a characteristic or belief of the person making the argument or claim, rather than by addressing the substance of the argument or producing evidence against the claim; an attempt to argue against an opponent's idea by discrediting the opponent himself. 2. A personal attack. (From: http://en.wiktionary.org/wiki/ad-hominem).

59. The charge of *ad hominem* argumentation is serious because such arguments are usually considered to be invalid. To clarify the record, it is acknowledged that the present Examiner has been purposefully blunt in considering the adequacy of the specification to support the pending claims. However, no argument or assertion has ever been made that the specification is inadequate, or that any argument is not persuasive, *because of any characteristic of the person who wrote the specification or made the argument*. Even the admittedly harsh expression "stumbled upon" was not directed to Applicant as a person, as the context clearly shows that subject at hand was the coincidental nature of the relationship between the results of Applicant's formula and the cell numbers taught in Strauer.

60. Since Applicant has chosen to broach the subject of *ad hominem* argumentation, the following excerpts from the record in this application are noted:

a. Present arguments, pages 46 and 51: This is a clear case of overreaching based on an apparent lack of knowledge.

b. Present arguments, pages 47, 51, and 52: Perhaps it is the lack of skill in the art that has led to the Examiner's failure to see any correlation between these examples and Applicant's overall regenerative cell therapy concept.

c. Present arguments, page 49: The present PTO Examiner, however, apparently does not possess the comparable skill and thus should accept the evidence proffered by those skilled the art, such as the Declarants.

61. Thus, the record shows that Applicant is in a poor position to be making accusations or complaining of *ad hominem* argumentation. Whether the present Examiner or any other examiner possesses knowledge or skill comparable to that of Applicant or Declarants is irrelevant. Valid, persuasive arguments must be addressed to the facts and arguments each party has put into the record.

62. In this regard, Applicant's repeated citation of *In re Neave*, 370 F.2d 961,152 USPQ 274; (CCPA 1967) is not persuasive. In that case, the declaration evidence relied on a subjective determination of color based on visual inspection and estimation. The court found that the ability to make this determination was an acquired skill of the expert and that determinations of this sort were routinely viewed as decisive and not mere opinion by persons of skill in the art. Thus, the court did not hold that all expert opinions should be accepted as fact, but only that in this particular case, the apparently subjective opinion of the expert should be accept as fact because this was the accepted practice in the art. The court further found that the same skill would not be

possessed by the examiner or the Board. Therefore, the expert's opinion was accepted as evidence of an unexpected result and the obviousness rejection written by the examiner and sustained by the Board was overturned (*In re Neave*, at 280). In the present case, Applicant asserts that the Declarants possess knowledge that is not possessed by the Examiner but Applicant cannot point to any decisive facts cited by Declarants that are not available to the Examiner. In the present case, nothing is based solely on the Examiner's opinion. Each finding that a Declarant's opinion is not persuasive to overcome the rejection of record is supported by facts and references. The rejection can only be overcome by countervailing facts, not by the mere assertion that the Examiner is not qualified to formulate an argument.

63. Applicant next addresses paragraphs 60-62 of the previous office action, which dealt with the subject of working examples. Applicant again points out that the rules permit reliance on prophetic examples. This has never been disputed. The question is whether the particular prophetic examples in the present specification are adequate to support enablement of the claims under consideration. Applicant then asserts:

> However, the PTO concludes, without further explanation, that the lack of actual examples "contribute significantly" to the determination of lack of enablement. It is the burden of the PTO to specifically and precisely point out why the absence of specific examples is a contributing factor.

64. The "without further explanation" is hard to understand as such explanation was the subject of the entirely of paragraphs 60-62. Paragraph 62 particularly pointed out that with respect to compliance with 35 USC 112, first paragraph, the entire claim has weight, including statements of purpose and intended outcome recited in the preamble or in 'wherein' clauses. Therefore, in the instant case, the claims must be enabled for forming and artery, growing new cardiac muscle, and repairing a dead or damaged portion of a heart. Several reasons were given as to why actual working examples would have been useful and why the prophetic examples fail

in providing guidance which has been found to be lacking in an unpredictable technology with respect to such matters as which cells to use, how many to use, when to administer the cells, and whether the disclosed results are confirmed by post-filing disclosures.

65. Applicant's further arguments on p.59 have been addressed in the record. See the previous office action at paragraph 61. It is herein reiterated that the PTO is not demanding a higher standard or employing a separate requirement for enablement because of the nature of the claimed invention.

66. Beginning on page 60, Applicant again addresses the declarations of Dr. Heuser and Dr. Lorincz. Most of Applicant's present arguments are repetitive of those which have been addressed in paragraph 63 of the previous office action. Applicant further argues:

> Contrary to the PTO's position, Applicant's evidence of enablement is supported by more than Declarants' conclusory statements. Declarants identify and rely upon facts, i.e., specific portions of the disclosure in the instant specification which support their conclusions that one skilled in the art would be able to make and use the claimed invention.

67. This is not persuasive because it has been shown in the record that the specific portions of the specification cited by Applicant and the Declarants contain numerous statements that cannot be reasonably characterized as "facts". Examples 11-17 do not set forth credible procedures to produce the results asserted within the examples, and they do not even mention growth of an artery or repair of a heart as recited in the instant claims. Bone marrow stem cells are not known to have the capability of differentiation and morphogenesis to form an entire organ, such as an eye, kidney or tooth, even under the influence of an electric spark or an expressed gene such as Aniridia or MSX-1. The prediction that "if germinal cells (and in some cases, stem cells) are utilized a direct differentiation and morphogenesis into an organ can occur in vivo, ex vivo, or in vitro" (specification p.48, lines 13-15) is, at best, mere speculation when the source of stem cells

is a mixed population of bone marrow cells and the organ under consideration is a new artery; the Ziegelhoeffer reference would suggest that this prediction is simply not born out. There is no evidence that new arteries are formed from structures that initially form in the absence of any connection to preexisting arteries as taught in prophetic Examples 18 (p.54), 19 (p.56) and 36 (p. 62); in fact post-filing evidence teaches the contrary (Buschmann, Augustin, Patan 723, and Patan 732). The general statement that organs and/or tissues can be formed utilizing the patient's own cells on page 47 of the specification can be accepted as fact, but even this is tainted by exemplification of a "patient's own cells" as a skin cell(s) is removed from the intraoral lining of a cheek and taken through a speculative and frankly incredible process of dedifferentiation and redifferentiation.

68. Therefore, the record fully supports the findings that "the Declarants merely managed to piece the general idea of the instant claims together" (re Applicants Argument, p.61) and that "the thread that connects the pieces of the generic concept also runs through hints of non-existent methods, unidentifiable cells, nonsensical method steps, and most importantly, predictions of results that are either incredible or directly contradicted by subsequent disclosures" (re Applicant Argument p. 62 and bridging pages 63-64).

69. On page 63 Applicant again compares the instant case to *in re Wands*, generally arguing that the "instant fact situation is similar to that of *In re Wands* because the skill level is also high and known administration techniques and known materials are also utilized in the practice of the invention." Again, Applicant's arguments are duplicative of those which were addressed in paragraph 65 of the previous office action, which finds that in the present case the only *Wands* factor weighing in favor of enablement is the level of skill in the art, which is relatively high.

70. Finally, Applicant's penultimate paragraph on page 64 takes issue with the citation of *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997) in the record. Applicant asserts:

> The Examiner seems to think that all that is required to support an enablement rejection is to repeat by rote case law without significant analysis establishing precedent vis a vis the evidence in chief relied on for a prima facie case

71. It is noted that paragraphs 66-68 of the previous office action were devoted to further explication of the expression "germ of an idea" as found in *Genentech* and applied to the present case. However, in response to Applicant's assertion, it is noted that like the present case, the question in *Genentech* was whether a patent contained sufficient detail concerning the practice of the claimed method. Genentech made the argument that the knowledge of one skilled in the art was sufficient to provide all of the missing information. Applicant has made the same argument; it has been argued herein and previously that in the present case the only *Wands* factor weighing in favor of enablement is the level of skill in the art, which is relatively high. Thus, there are ample parallels between the present case and *Genentech*. The court held that Genentech's arguments were focused almost exclusively on the level of skill in the art and ignored the essence of the enablement requirement. "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (*Genentech v. Novo Nordisk A/S* at 1005).

72. The rejection of record has given careful consideration to the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the level of skill in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. It has been acknowledged that the level of skill in the art is high. However, the remaining factors indicate that the each of

the claims under consideration must be rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Conclusion

73. No claim is allowed

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel C Gamett/
Examiner, Art Unit 1647

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646